

# Pulse Steroid Therapy

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## ABSTRACT

Intravenous supra-pharmacological doses of corticosteroids are used in various inflammatory and autoimmune conditions because they are cumulatively less toxic than sustained steroid treatment at lower quantitative dosage. Their action is supposed to be mediated through non-genomic actions within the cell. Common indications for use in children include steroid resistant and steroid dependent nephrotic syndrome, rapidly progressive glomerulonephritis, systemic vasculitis, systemic lupus erythematosus, acute renal allograft rejection, juvenile rheumatoid arthritis, juvenile dermatomyositis, pemphigus, optic neuritis, multiple sclerosis and acute disseminated encephalomyelitis. Methylprednisolone and dexamethasone show similar efficacy in most conditions. Therapy is associated with significant side effects including worsening of hypertension, infections, dyselectrolytemia and behavioral effects. Adequate monitoring is essential during usage. [Indian J Pediatr 2008; 75 (10): 1057-1066] E-mail: arvind bagga@hotmail.com

**Key Words:** High dose corticosteroid; Dexamethasone; Methylprednisolone

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Glucocorticoids have been used for the management of inflammatory diseases since the last 50 years.<sup>1</sup> In most of the conditions where steroids are indicated, the oral route is preferred, in the minimum dose required to keep the disease state in remission. The first reported use of high dose intravenous (i.v.) corticosteroids was in 1969 when it was used to successfully prevent renal allograft rejection<sup>2</sup>. High dose i.v. corticosteroid therapy or "pulse" steroid therapy was first used for treatment of acute rejection after kidney transplantation in 1973, for the treatment of lupus nephritis in 1976 and in steroid resistant nephrotic syndrome later<sup>3-6</sup>.

The 'big shot', as it was termed in an early editorial, has since come to be used in a variety of inflammatory, autoimmune and renal diseases<sup>7</sup>. However, there are considerable variations in the dose, number, timing and duration of administration of high dose i.v. corticosteroids. Also, despite more than three decades of use, there is little clarity on the mechanism of action, magnitude of benefits and adverse effects. Here, we summarize the current literature on high dose i.v. corticosteroid therapy, including indications, dosages and regimes used and the proposed mechanisms of action.

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## DEFINITION

Pulse therapy means the administration of supra-pharmacologic doses of drugs in an intermittent manner to enhance the therapeutic effect and reduce the side effects<sup>8-9</sup>. In context of corticosteroids, pulse therapy refers to discontinuous i.v. infusion of high doses of the medication, arbitrarily defined as treatment with more than 250 mg prednisone or its equivalent per day, for one or more days<sup>10</sup>.

There are no guidelines on the frequency or timing of administration of the i.v. pulses; which therefore includes single boluses, daily boluses given for 3 days in a row, or on alternate days for up to 12 days<sup>3-7,9</sup>.

## MEDICATIONS USED

The agent most commonly used for corticosteroid pulse therapy is methylprednisolone (MP), which is derived following chemical modification of hydrocortisone<sup>11</sup>. Methylprednisolone is an intermediate acting (biological half life of 12-36 hours), potent, anti-inflammatory agent (potency 1.25 times compared to prednisolone), with a low tendency to induce sodium and water retention (relative glucocorticoid to mineralocorticoid effect 6:1) compared to hydrocortisone<sup>12</sup>.

Dexamethasone, a fluoridated glucocorticoid, is a long acting agent (biological half life of 36-72 hours). It is 6.7 times more potent than prednisolone, has negligible mineralocorticoid effect with almost no sodium retaining tendency, and a small equipotent volume.<sup>12-13</sup> Dexamethasone has been used for pulse therapy in diverse clinical conditions with favorable results.<sup>14-20</sup> Therapy with this drug is less expensive as compared to methylprednisolone [methylprednisolone (Solumedrol) Rs. 990 for 1 g, Rs. 657 for 500 mg, dexamethasone (Decamycin) Rs. 160 for 200 mg]. For example, for a child weighing 20 kg, the cost of therapy with 6 pulses of dexamethasone is Rs. 500 while that with methylprednisolone is Rs. 4400. However, the difference in cost has decreased over the years.

### DOSAGE AND ADMINISTRATION

The doses initially used in adults, 1-2 g of methylprednisolone, were based on a study in normal adult male volunteers to determine a safe dose for treating traumatic shock, and the same was translated into doses of up to about 30 mg/kg in children<sup>21</sup>. Methylprednisolone is administered at a dose of 20-30 mg/kg (500-1000 mg/m<sup>2</sup>) per pulse; up to a maximum dose of 1 g. Dexamethasone is administered at a dose of 4-5 mg/kg (100-200 mg) per pulse.

Initially the duration of infusion was based on a study in normal adults, and was 10 to 20 minutes.<sup>21</sup> However, rapid infusions are known to be associated with a higher risk of hemodynamic abnormalities, and hence administration over 1-3 hours is preferred.<sup>22</sup> The corticosteroid preparation is dissolved in 150-200 ml of 5% dextrose and infused intravenously, slowly over 2-3 hours.

Repeat pulses are given at intervals of 24-48 hours, *i.e.*, daily or on alternate days, usually for three or six pulses. Subsequently, the interval between pulses is progressively increased to weekly, fortnightly or monthly administration.

### PHARMACOKINETICS

Methylprednisolone and dexamethasone have high bioavailability, are bound primarily to serum albumin, and are widely distributed to the tissues.<sup>12</sup> Both agents are minimally bound to transcortin and the unbound "free" concentration of the drugs, following intravenous administration is high. Dexamethasone has more potent anti-inflammatory activity than methylprednisolone, because of its increased affinity for glucocorticoid receptors and less protein binding.<sup>11, 12</sup> Methylprednisolone may have the advantage of a

quicker penetration of the cell membrane compared to dexamethasone.<sup>23</sup>

Intravenous methylprednisolone shows a rapid peak with a subsequent serum half life of 3 hours. A large proportion of the bolus rapidly enters the gut, manifested by the appearance of a metallic taste; it then reenters the venous space via the splanchnic circulation causing a secondary peak in the serum level. The drug is demethylated in the liver to become pharmacologically active as prednisolone. Studies in children have shown similar kinetics, but with up to 5 fold variations in serum half-lives.<sup>24</sup> Unlike methylprednisolone, dexamethasone has no pre-systemic metabolism.

There is lack of evidence to suggest that the intravenous route is preferable to the oral route. Studies show equivalent therapeutic responses in patients with multiple sclerosis and rheumatoid arthritis after oral and intravenous administration of the same high dose of pulsed methylprednisolone.<sup>25-26</sup> However, patients had nausea and malaise lasting several hours with oral prednisolone.<sup>25-26</sup> A comparison of pharmacokinetics of oral and intravenous high dose dexamethasone revealed a mean bioavailability of 63.4% for oral therapy.<sup>27</sup> However, bioavailability levels reported in the literature for oral low-dose dexamethasone show wide variation (53-100%).<sup>28</sup>

### RATIONALE FOR USE OF HIGH DOSE INTRAVENOUS GLUCOCORTICOIDS

The aim of pulse therapy is getting quicker and stronger efficacy and decreasing the need for long-term use of steroids. The paradox here is that administration of high dose steroids is used to achieve the steroid-sparing effect.

The largest experience with pulse therapy has been reported in patients with pemphigus. Pasricha *et al* described steroid-sparing effects and long-term remission extending up to 9 years<sup>14</sup>. Many studies have demonstrated the efficacy and safety of pulse therapy in various disorders; toxicity has been consistently reported to be less than that seen with daily oral prednisone<sup>3-6, 9, 21-22</sup>. When corticosteroids are administered as pulses, an immediate profound anti-inflammatory effect is achieved and the toxicities seen with conventional high dose oral therapy are low. There is a faster clinical recovery from symptoms than with oral therapy, and therefore inflammatory damage is minimized. The clinical improvement is seen to last about 3 weeks after one pulse, and there is no prolonged suppressive effect on the hypothalamic-pituitary axis<sup>21</sup>. Hence pulse therapy has a favourable risk/benefit ratio and shows considerable efficacy in

short term control of inflammation. Although pulse steroid therapy may provide symptomatic relief in inflammatory diseases, it might not change the long term course of any specific disease.

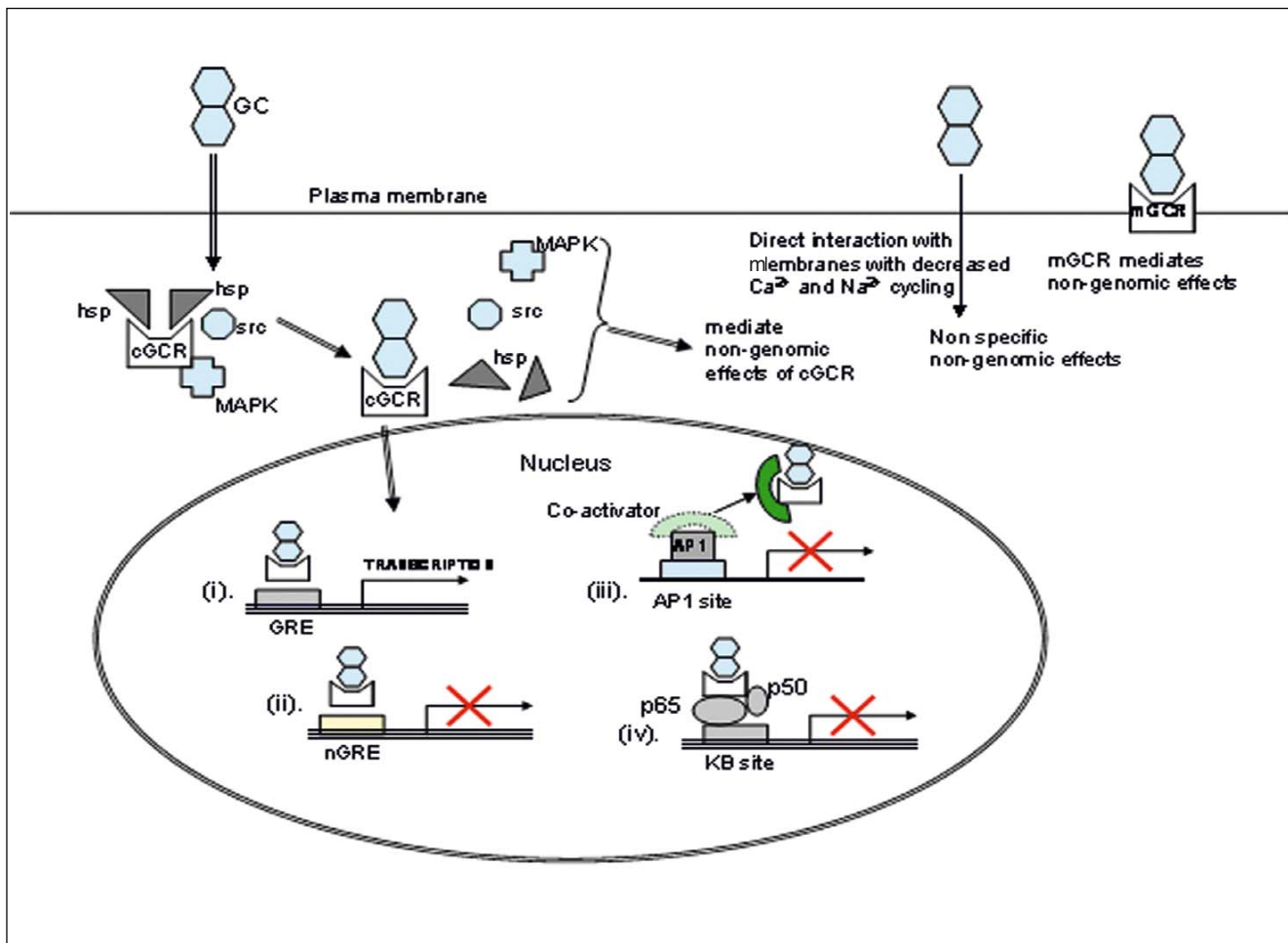
## MECHANISM OF ACTION

Glucocorticoids exert a variety of immunosuppressive, anti-inflammatory and anti-allergic effects on primary and secondary immune cells and tissues.<sup>12</sup> Studies have shown that the cellular effects of glucocorticoids are mediated by genomic and various nongenomic

mechanisms (see Fig. 1).<sup>1, 29-30</sup>

## Genomic effects

Within the cell, glucocorticoids form complexes with specific cytosolic glucocorticoid receptors (cGCR) which is a multiprotein complex containing several heat-shock proteins (hsp70 and hsp90), and has a zinc-finger motif needed for transcription function. The cGCR also interacts with immunophilins, co-chaperones such as p23 and src, and several kinases of the mitogen-activated protein kinase (MAPK) signaling system. The activated glucocorticoid receptor complex moves to the nucleus, binds as a homodimer to a



**Fig. 1. Genomic and nongenomic effects of glucocorticoids (GC).** GC pass through cytoplasmic membrane to bind to the cytosolic glucocorticoid receptor (cGCR), displacing several associated proteins (heat shock proteins hsp, kinases like mitogen activated protein kinase/MAPK and co-chaperones like src) that mediate nongenomic effects. The GC-cGCR complex moves into the nucleus to affect transcription by ways depicted above. (i) and (ii) involve binding of cGCR to positive and negative glucocorticoid responsive elements (GRE and nGRE); in (iii) binding of cGCR is prevented by competition for nuclear coactivators between the cGCR and transcription factors like activator protein 1 (AP1); (iv) involves transrepression due to direct or indirect interaction of the cGCR with transcription factors such as nuclear factor-kB (NF-kB) at its binding site (KB site). Non-genomic effects are also suggested to be mediated through membrane bound GCR (mGCR) and by interactions with cellular membranes.

specific DNA sequences in the promoters of the genes that it will affect (glucocorticoid responsive elements, GRE), and activates transcription factors, thus causing inhibition or induction of transcription, translation and finally the synthesis of specific regulator proteins. Induction of transcription *via* positive GRE is termed "transactivation". Inhibition of transcription can occur *via* direct interaction between the GCR and negative GRE, or, transcription factors can be displaced from the positive GRE through direct protein-protein interaction between transcription factors and the GCR. These direct positive and negative gene modulations affect proteins like cytokines, chemokines, inflammatory enzymes and adhesion molecules, resulting in modification of inflammation and immune response mechanisms. In another genomic mechanism termed "transrepression", monomers of the glucocorticoid/GCR complex directly or indirectly interact with transcription factors. One example is the induction of synthesis of I $\kappa$ B, which decreases the amount of the pro-inflammatory transcription factor NF- $\kappa$ B that could translocate to the nucleus and activate transcription of genes for IL-1, IL-6, and TNF- $\alpha$ . The effects of genomic action are not immediate; it usually takes hours or days before changes on cellular or tissue level become evident.

### Non-genomic effects

Nongenomic glucocorticoid activities can be subclassified further into three modes of action: cGCR-mediated non-genomic effects; non-specific non-genomic effects (e.g., physicochemical interactions with plasma membrane at high glucocorticoid concentrations); and effects that are considered to be mediated by membrane-bound glucocorticoid receptors (Fig. 1).

The binding of glucocorticoids to the cGCR-associated multi-protein complex leads to rapid intracellular signaling through other components of the complex like the co-chaperone src and MAPK. At high concentrations, glucocorticoid molecules intercalate into cell membrane, which alters cellular functions by influencing cation transport *via* the plasma membrane and by increasing the proton leak of the mitochondria. These result in reduced calcium and sodium cycling across plasma membranes of immune cells, which is thought to contribute to rapid immunosuppression and a subsequent reduction of the inflammatory process. Glucocorticoid receptors have been found to be expressed on cell membranes of human cells (mGCR); mGCR-mediated mechanism may be involved in the rapid induction of apoptosis, and induction of lipomodulin, which inhibits production of prostaglandins and leukotrienes.

### Effects of high dose intravenous/pulse steroids

The immunosuppressive clinical effects observed when high dose glucocorticoids are administered

intravenously occur too rapidly to be explained by the classic (genomic) mechanism of action alone. Evidence suggests that high *in vivo* levels of steroids obtained by pulse corticosteroid therapy have qualitatively different pharmacologic effects than those produced at lower doses. High doses of glucocorticoids have been shown to inhibit NF- $\kappa$ B action (transrepression) only at concentrations within the cell obtainable by the highest oral or intravenous doses.<sup>30</sup> Buttgerit *et al* have postulated 3 "modules" of glucocorticoid effect on cells resulting from different concentrations: (i) low concentrations mediate effects *via* genomic events; (ii) medium concentrations bind as well to cell surface receptors, which activate cross membrane signal transmission for genomic and non-genomic intracellular events; and (iii) at very large concentrations steroids dissolve in the cell membrane resulting in greater membrane stability and reduced non-genomic cell function generally.<sup>29</sup>

A single glucocorticoid application at a high dose has a strong effect due to 100% saturation of cytosolic receptors; however, the effect would last only for a short period because receptor occupation rapidly reverts to the original value unless a new dose is given.<sup>12</sup> Therefore, a single high dose is unlikely to have sustained effect.

Overall, the effects of corticosteroid pulses appear to include downregulation of activation of immune cells and proinflammatory cytokine production, leading to reduced expression of adhesion molecules and reduced movement of neutrophils into sites of inflammation. These effects are qualitatively similar to those seen with anti-TNF-alpha therapy.<sup>31</sup>

## INDICATIONS FOR USE

Since its first use in prolonging renal allograft survival in adults, high dose intravenous steroids have come to be used in a variety of conditions in children as well. There is considerable experience reported in the field of pediatric nephrology, particularly in nephrotic syndrome, renal allograft rejection, lupus nephritis and crescentic glomerulonephritis; other uses have included Kawasaki disease and Henoch Schonlein purpura. Dermatologists have successfully used this therapy in skin diseases like pemphigus, Reiter's disease and pyoderma gangrenosum<sup>20</sup>. It is accepted as an established therapy for rheumatoid arthritis, including systemic juvenile rheumatoid arthritis and other inflammatory conditions like juvenile dermatomyositis and leukocytoclastic vasculitis. The indications for which high dose intravenous steroids are



## Pulse Steroid Therapy

used are outlined in Table 1, and discussed below.

### Steroid resistant nephrotic syndrome

Several protocols using intravenous methylprednisolone, cyclophosphamide and cyclosporin A have been used for induction of remission in steroid resistant nephrotic syndrome due to minimal change disease, mesangial proliferative glomerulonephritis and focal segmental glomerulosclerosis (FSGS). Mendoza *et al* treated 32 patients of steroid resistant focal segmental glomerulosclerosis with intravenous methylprednisolone and alkylating agents and found a favorable response in 75% patients<sup>6</sup>. Other studies using similar therapy in patients with steroid resistant FSGS showed a variable response ranging from 0-72.7%. Hari *et al* compared the short term efficacy of intravenous methylprednisolone and dexamethasone in this disease, and reported complete remission in 20 (35.1%) patients in dexamethasone and 7 (33.1%) patients in methylprednisolone group<sup>15</sup>. The protocol involves administration of six pulses of 30 mg/kg (maximum 1 g) of methylprednisolone or 5 mg/kg (maximum 150 mg) of dexamethasone on alternate days, followed by 4 fortnightly pulses and 8 monthly pulses, along with tapering doses of oral prednisolone on alternate days over 52 weeks, with or without oral cyclophosphamide for 12 weeks<sup>6, 15</sup>.

### Steroid dependent nephrotic syndrome

Pulsed administration of steroids is often used for the

rapid induction of remission in patients with steroid sensitive nephrotic syndrome, where features of steroid toxicity are prominent and prolonged administration of high doses of oral steroids is not rational, *e.g.*, in presence of markedly cushingoid body habitus, or presence of steroid induced cataracts. Four to six pulses of methylprednisolone at 20-30 mg/kg or dexamethasone at 4-5 mg/kg are administered, daily or on alternate days; following remission, therapy with oral prednisolone at 1-2 mg/kg is continued.

### Rapidly progressive glomerulonephritis and vasculitis

Patients presenting clinically as rapidly progressive glomerulonephritis and with renal biopsy suggestive of crescentic glomerulonephritis ( $\geq 50\%$  glomeruli with crescents) are administered 4-6 pulses of methylprednisolone at 20-30 mg/kg or dexamethasone at 4-5 mg/kg, daily or on alternate days, followed by intravenous cyclophosphamide 500-750 mg/m<sup>2</sup> once a month for 6 months, along with oral prednisolone at 1-2 mg/kg on alternate days.

Remission in patients with systemic vasculitis and generalized organ-threatening disease is induced with pulse cyclophosphamide with oral corticosteroids. Patients with rapidly progressive renal failure, with and without diffuse alveolar hemorrhage, are usually administered daily pulses of corticosteroids and intravenous cyclophosphamide as outlined above. Plasma exchange is used as adjunct to the above therapy in advanced renal disease<sup>32</sup>.

TABLE 1. Indications for High Dose Intravenous Steroid Therapy

System	Commonly indicated in	Infrequently used in
Musculoskeletal diseases	Rheumatoid arthritis Juvenile rheumatoid arthritis	Psoriatic arthritis Ankylosing Spondylitis
Collagen vascular diseases	Systemic lupus erythematosus Systemic dermatomyositis (polymyositis) Severe forms of vasculitis	Systemic sclerosis Kawasaki disease Henoch Schonlein purpura
Renal diseases	Steroid resistant nephrotic syndrome Crescentic glomerulonephritis Vasculitis with active nephritis Acute allograft rejection	Steroid sensitive nephrotic syndrome Lupus nephritis
Dermatologic diseases	Pemphigus vulgaris Bullous dermatitis herpetiformis Severe psoriasis Alopecia totalis	Severe Stevens-Johnson syndrome Pyoderma gangrenosum Vitiligo with rapidly progressive disease Exfoliative dermatitis
Ophthalmic diseases	Optic neuritis Uveitis in multiple sclerosis Corneal allograft rejection	Traumatic optic neuropathy Vogt- Koyanagi-Harada disease Posterior segment uveitis in Behçet's disease
Hematologic disorders	Acquired (autoimmune) hemolytic anemia Idiopathic thrombocytopenic purpura	Autoimmune hemolytic anemia Acquired aplastic anemia
Neurological diseases	Acute disseminated encephalomyelitis Acute exacerbations of multiple sclerosis	Myasthenia gravis
Neoplastic diseases		Palliative management of acute leukemia or non Hodgkin's lymphoma
Pulmonary diseases	Acute respiratory distress syndrome	
Gastrointestinal diseases	Acute hepatic cellular rejection	Severe ulcerative colitis

### Systematic lupus erythematosus (SLE)

Therapy in patients with severe lupus nephritis (including WHO class III, IV, III+V, or IV+V) and severe acute non-renal disease, e.g. acute hemolytic anemia, uveitis, pericarditis or CNS lupus, comprises methylprednisolone pulses for three to five days, followed by six monthly pulses of cyclophosphamide (CP) along with oral prednisone at 1.5 mg/kg per day. In the maintenance phase therapy is continued with azathioprine or mycophenolate mofetil along with oral prednisolone on alternate days. In a double blinded, randomised controlled trial in 82 patients with lupus nephritis, Gourley *et al* demonstrated that the combination of IV CP and IV methylprednisolone was more effective in inducing remission (renal remission 85%) than therapy with either alone.<sup>33</sup>

However, a recent retrospective study conducted in adults questions the need of administration of high doses of methylprednisolone in treating SLE flares; here, administration of lower doses of methylprednisolone (total dose 1-1.5 g in three days) showed similar efficacy and was associated with decreased risk of infections when compared to standard higher doses (3 g in three days).<sup>34</sup>

### Acute renal allograft rejection

In the setting of acute renal allograft dysfunction when a diagnosis of acute rejection is made (graft biopsy suggestive of acute rejection Banff 1A / Banff 1B), methylprednisolone is administered intravenously at 10-15 mg/kg daily for 5 days followed by oral prednisolone daily at 2 mg/kg which is subsequently tapered; concomitant immunosuppression (tacrolimus/cyclosporine/azathioprine/mycophenolate mofetil) is often increased. However, a recent study suggests that therapy with just 3 mg/kg per day of intravenous methylprednisolone for 3 consecutive days is as effective as 15 mg/kg per day of methylprednisolone in reversing acute renal allograft rejection (80% vs 68%; 95% confidence intervals of the difference -8% to 32%).<sup>35</sup>

### Juvenile rheumatoid arthritis

In patients with juvenile rheumatoid arthritis, pulsed administration of steroids is often used, especially in refractory cases with serious systemic features. It is often used to cause rapid improvement while simultaneously adding a slower acting disease modifying drug, *i.e.*, as "bridge" therapy while awaiting the effects of the latter drug. Three pulses are given daily or on alternate days, or monthly pulses are administered, while adding alternate day oral prednisolone at 1-2 mg/kg and nonsteroidal antiinflammatory agents, and instituting therapy with hydroxychloroquine, methotrexate or azathioprine. Its efficacy and toxicity is similar to that of infliximab.<sup>36</sup> Aghighi *et al* studied the efficacy of methylprednisolone pulses in 120 children

with juvenile rheumatoid arthritis, and noted that therapy was associated with significant improvement in the number of swollen and tender joints, duration of morning stiffness, erythrocyte sedimentation rate, C-reactive protein and hemoglobin levels; the mean duration of disease remission was  $3.3 \pm 0.7$  months.<sup>37</sup>

### Juvenile dermatomyositis

Methylprednisolone pulses as initial therapy may be effective in preventing the chronicity and recurrence of juvenile dermatomyositis. If indicators of inflammation (*e.g.*, CD56+ NK cell count, neopterin, vWF Ag) are high, intravenous methylprednisolone is administered at 20 mg/kg for 1-3 days, followed by further treatment twice a week for 2 to 5 weeks, along with oral prednisolone at 1-2 mg/kg on alternate days. If patients fail to achieve normal muscle strength over 4 months, muscle enzymes over 3 months and normalized vWF over 10 months, the probability of their disease following a chronic course is higher.<sup>38</sup> Using a retrospective, nonrandomized design with propensity score matching to compare aggressive (intravenous methylprednisolone or oral prednisone 5-30 mg/kg/day) *versus* standard (oral prednisolone 1-2 mg/kg/day) therapy in 139 patients with juvenile DM, Sheshadri *et al* found little difference in outcomes between aggressive and standard therapy. It should be noted that the sickest patients were treated with aggressive therapy and were not included in the matched analysis.<sup>39</sup>

### Acute disseminated encephalomyelitis (ADEM)

ADEM is a monophasic demyelinating disease involving the central nervous system. Therapy with high dose intravenous steroids, administered as 30 mg/kg of methylprednisolone daily for 3-5 days followed by daily oral prednisolone at 1 mg/kg for ten days results in clinical improvement. Recovery without disability is seen in over 70% patients at 6 months follow up.<sup>40</sup>

### Multiple sclerosis (MS)

Although the condition is rare in children below ten years of age, therapy with methylprednisolone has an important role particularly in the acute phase of the disease. High doses of intravenous methylprednisolone have been shown to be effective in reducing the number of MRI contrast-enhanced lesions at 30 and 60 days, mainly by decreasing the rate of new lesion formation.<sup>41</sup>

### Optic neuritis

The Optic Neuritis Treatment Trial (ONTT) showed that the administration of high dose steroids may reduce the risk of progression of optic neuritis to MS by more than 50% up to 2 years.<sup>42</sup> In adults, intravenous dexamethasone 200 mg once daily for three days or

intravenous methylprednisolone 250 mg six-hourly for three days followed by oral prednisolone is the usual prescription.<sup>42</sup>

### Pemphigus

Dexamethasone cyclophosphamide pulse (DCP) therapy is used for treatment of pemphigus in adults. Each course of therapy consists of 100 mg dexamethasone given daily for three days, along with 500 mg cyclophosphamide on day 2. The course is repeated at 4-weekly intervals for six months, while 50 mg cyclophosphamide is given orally daily during throughout this period.<sup>8, 14</sup>

### EFFICACY OF DEXAMETHASONE COMPARED TO METHYLPREDNISOLONE

While few studies have prospectively compared the efficacy of intravenous methylprednisolone to dexamethasone, they seem to suggest that the two agents are equally efficacious in management of various conditions, including optic neuritis, traumatic optic neuropathy, acute endothelial graft rejection after corneal transplant, multiple sclerosis and steroid resistant nephrotic syndrome.<sup>15-17, 43-44</sup> A comparison of efficacy of intravenous dexamethasone to methylprednisolone in 21 patients with optic neuritis showed no significant differences between the two groups in terms of color vision, contrast sensitivity, stereoacuity and visual fields at 90 days of therapy.<sup>44</sup> A double blind trial in 31 patients with multiple sclerosis showed that intravenous dexamethasone and high dose methylprednisolone have similar efficacy in promoting recovery from acute relapses of the disease.<sup>43</sup> Both dexamethasone and methylprednisolone significantly decreased severity of symptoms, and resulted in 2-3 fold decrease in disease activity, in a trial involving 31 patients with rheumatoid arthritis; side effects of therapy were minimal in both groups.<sup>17</sup> A study reporting the short term efficacy of these two agents in patients with steroid resistant nephrotic syndrome showed similar rates of complete remission (35.1% with dexamethasone and 33.1% with methylprednisolone), similar reduction in the urine protein creatinine ratio (54.1% with dexamethasone and 63.2% with methylprednisolone) and similar side effect profile.<sup>15</sup>

### CONTRAINDICATIONS

Systemic infections, including fungal sepsis and uncontrolled hypertension are contraindications to initiation of pulse steroid therapy. The therapy is also contraindicated in patients with known hypersensitivity to the steroid preparation.

### ADVERSE EFFECTS

Intravenous pulse steroids have been associated with potentially serious complications. Mild hypotension was known to occur in normotensive children in days when relatively rapid infusions were used. The most significant serious effects in children are increased blood pressure in already hypertensive children during and after the infusion, seizures, particularly in systemic lupus erythematosus, which may be related to rapid flux in electrolytes, and anaphylactic shock after even one prior infusion, usually associated with the succinate ester of methylprednisolone.<sup>45</sup> Abnormal behavior (including mood alteration, hyperactivity, psychosis, disorientation, sleep disturbances) is a common acute adverse effect, being seen in about 10% patients.<sup>46</sup> Hyperglycemia, hypokalemia and infections are other common adverse effects. Higher cumulative doses of methylprednisolone (>5 g) confer a higher risk of infection.<sup>47</sup>

The overall incidence of side effects with intravenous pulse therapy may exceed 50%.<sup>46</sup> Most steroid effects, such as cushingoid facial appearance are not as severe as with daily steroid therapy.

Sudden death, cardiac arrhythmias, circulatory collapse and cardiac arrest have been reported occasionally, usually following rapid administration of large doses of methylprednisolone (>500 mg administered over <10 minutes)<sup>45-46</sup>. Bradycardia may occur unrelated to the speed or duration of infusion. Overall, arrhythmias may occur in 1% to 82% of patients, after single or daily doses, and their onset may occur during administration of therapy or several days later; and though most reports are in adults, they have occurred in pediatric patients.<sup>45-46</sup>

In a study in juvenile rheumatoid arthritis, complications noted included tachycardia (13.3%), hypertension (8.3%), headache (1.7%), and flushing (1.7%).<sup>37</sup> The chief side effect noted in a comparative study of methylprednisolone and dexamethasone in patients with steroid resistant nephrotic syndrome as transient hypertension or worsening of preexisting hypertension (52.5% in dexamethasone group; 45.5% in methylprednisolone group). Other side effects were infrequent and comparable in the two groups, including serious infections (3 out of 91 patients), hyperglycemia (2 patients) and asymptomatic dyselectrolytemia (hypokalemia and hyponatremia in 10 and 11 patients respectively); one or more side effects were observed in 66.7% children receiving dexamethasone therapy and 61.9% receiving methylprednisolone.<sup>15</sup>

Few reports exist on the metabolic effects of pulse therapy. Cortisol levels decrease initially but return to normal levels within 24-48 hr after infusions. A general

belief has been that short courses of pulse intravenous MP do not result in long term bone density changes. However, recently, Haugeberg *et al* have suggested that treatment with intravenous pulses of MP leads to a high rate of bone loss that cannot be ignored.<sup>48</sup> There are reports of avascular necrosis of the hip, but a retrospective study failed to find an increased risk of the osteonecrosis in patients with rheumatoid arthritis treated with pulse steroids.<sup>49</sup> Similarly Zonana-Nacach *et al* studied a cohort of 539 patients with SLE and found no association between IV steroid therapy and avascular necrosis, but did with high dose oral steroids; the cumulative prednisolone dose was associated with osteoporotic fractures, coronary artery disease and cataracts, stroke was associated with high-dose prednisolone, and the only statistically significant association with IVmethylprednisolone was cognitive dysfunction.<sup>50</sup>

### General principles of administration and monitoring for adverse events

These are outlined in Table 2.

### CONCLUSION

Pulses of high doses of corticosteroids have a

significant but transient anti-inflammatory effect. Not all effects are well understood, and some effects may have unique pharmacologic properties not related to exaggerating mechanisms obtained with lower doses. When used in appropriate diseases and circumstances, large intravenous pulses of corticosteroid are cumulatively less toxic than sustained steroid treatment at lower quantitative dosage, but no evidence exists that by themselves they can cure or alter long term outcomes in diseases. More information is needed to define the specific diseases to be treated, the optimal steroid to be used, and the optimal timing of pulses to avoid chronic toxicity and obtain maximum benefit.

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TABLE 2. Protocol for High Dose Intravenous "Pulse" Steroids Administration

ADMINISTRATION OF INTRAVENOUS HIGH-DOSE CORTICOSTEROIDS	
<b>Medication used</b>	
Methylprednisolone (20-30 mg/kg) or dexamethasone (4-5 mg/kg)	
<b>Route and method of administration</b>	
The corticosteroid preparation is dissolved in 150-200 ml of 5% dextrose and infused intravenously, slowly over 2-3 hours.	
<b>Precautions</b>	
<i>A. Before starting therapy</i>	
The patient should be free from any systemic infections before administration of corticosteroids. Minor upper respiratory tract, gastrointestinal or skin infections are not a contraindication to therapy.	
Blood pressure must be controlled using appropriate drugs.	
Obtain total and differential white cell counts, and blood level of sugar, urea, creatinine, sodium and potassium.	
<i>B. During and following therapy</i>	
Careful record of heart rate, respiratory rate and blood pressure every 15-30 minutes should be maintained.	
If an arrhythmia is suspected, the infusion is discontinued; an ECG and blood levels of sodium, potassium, calcium and magnesium are obtained and abnormalities are rectified.	
Careful screening for occurrence or exacerbation of infections.	
Estimate blood levels of sugar and electrolytes every other day.	



## Pulse Steroid Therapy

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